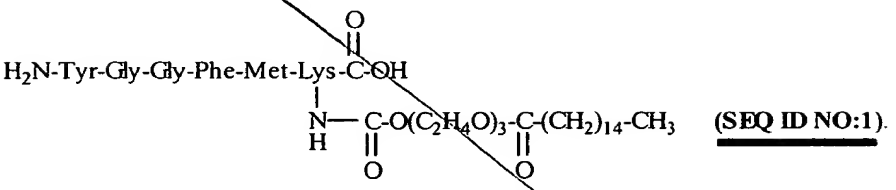
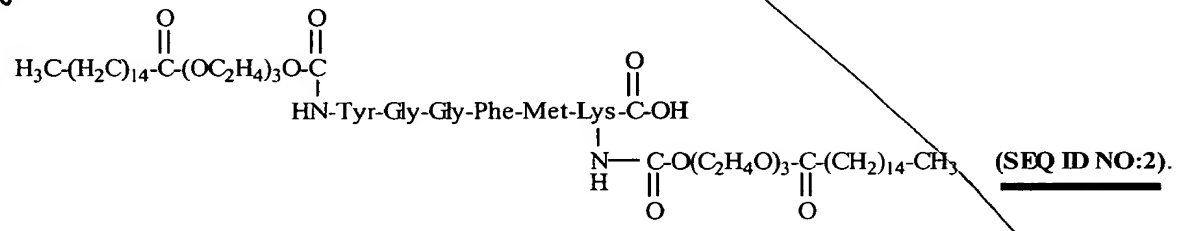


(SEQ ID NO:1).

97. (Amended) The method of claim 46 wherein the drug-oligomer conjugate has a formula:



(SEQ ID NO:2).

REMARKS

The amendments above conform the specification and claims to the requests contained in the Office Action mailed January 18, 2001. Marked-up versions of the substituted paragraphs are provided at Appendix A.

Applicants have also taken this opportunity to correct various typographical errors in the specification. For example, at page 25, line 1, the term "Trp-Pro-Lys-His-Xaa-NH_2" has been replaced with the term --Trp-Trp-Pro-Lys-His-Xaa-NH_2-- in order to correct a typographical error. If required, support for this amendment can be found at column 1, line 66-67 of U.S. Patent No. 5,641,861, which was incorporated by reference in the present application.

Applicants have also amended Figures 2-8 to reference sequence ID numbers as requested by the Examiner. Amended Figures 2-8 are enclosed herein.

Any questions regarding the foregoing should be directed to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: BOX SEQUENCE Commissioner for Patents, Washington, DC 20231, on February 20, 2001.

J. Michael Strickland
Date of Signature: February 20, 2001

APPENDIX A

Marked-Up Replacement Paragraphs

The paragraph beginning at page 24, line 28 has been amended as follows:

In another **[other]** aspect, the therapeutic peptide of the amphiphilic drug-oligomer conjugates are as described in United States Patent 5,641,861, which is incorporated herein by reference, so long as any of such peptides contains a lysine residue. Exemplary peptides described therein include: Ac-Phe-Arg-Trp-Trp-Tyr-Lys—NH_2 **(SEQ ID NO:4)**; Ac-Arg-Trp-Ile-Gly-Trp-Lys—NH_2 **(SEQ ID NO:5)**; Trp-Trp-Pro-Lys-His-Xaa—NH_2 **(SEQ ID NO:6)**, where Xaa can be any one of the twenty naturally occurring amino acids, or Trp-Trp-Pro-Xaa—NH_2 **(SEQ ID NO:7)**, where Xaa is Lys or Arg; Tyr-Pro-Phe-Gly-Phe-Xaa—NH_2 **(SEQ ID NO:8)**, wherein Xaa can be any one of the twenty naturally occurring amino acids; (D)Ile-(D)Met-(D)Ser-(D)Trp-(D)Trp-Gly_n-Xaa—NH_2 **(SEQ ID NO:9)**, wherein Xaa is Gly or the D-form of a naturally-occurring amino acid and n is 0 or 1, peptides of this formula can be hexapeptides when Gly is absent (n is 0) and heptapeptides when Gly is present (n is 1); (D)Ile-(D)Met-(D)Thr-(D)Trp-Gly-Xaa—NH_2 **(SEQ ID NO:10)**, wherein Xaa is Gly or the D-form of a naturally-occurring amino acid; Tyr-A1-B2-C3—NH_2 **(SEQ ID NO:11)**, wherein A1 is (D)Nve or (D)Nle, B2 is Gly, Phe, or Trp, and C3 is Trp or Nap; Pm and red {Me_xH_yN-Tyr-$(NMe)_z$-Tyr-Xaa_z—NH_2} **(SEQ ID NO:12)**, wherein x and y independently are 0,1, or 2 and z is 0 or 1, and wherein Xaa is Phe, D-Phe, or NHBzl; Trp-Trp-Pro-D4-His_z-Xaa_z-NH_2 **(SEQ ID NO:13)**, wherein z is 0 or 1, D4 is Lys or Arg and Xaa is any one of the naturally-occurring amino acids.

The paragraph beginning at page 25, line 12 has been amended as follows:

In still another **[other]** aspect, the therapeutic peptide of the amphiphilic drug-oligomer conjugates are as described in United States Patent 5,602,099, which is incorporated herein by reference. with the proviso that the conjugation can occur only where there is a free carboxyl or free N-terminal. Exemplary peptides include: H-Tyr-Tic-Phe-Phe-OH **(SEQ ID NO:14)**; H-Tyr-Tic-Phe-Phe-NH_2 **(SEQ ID NO:15)**; Tyr(NαMe)-Tic-Phe-Phe-OH **(SEQ ID**

NO:16); Tyr(NαCpm)-Tic-Phe-Phe-OH **(SEQ ID NO:17)**; Tyr(NαHex)-Tic-Phe-Phe-OH **(SEQ ID NO:18)**; Tyr(NαEt_2)-Tic-Phe-Phe-OH **(SEQ ID NO:19)**; H-Dmt-Tic-Phe-Phe-OH **(SEQ ID NO:20)**; H-Dmt-Tic-Phe-Phe-NH_2 **(SEQ ID NO:21)**; H-Tyr(3-F)-Tic-Phe-Phe-OH **(SEQ ID NO:22)**; H-Tyr(3-Cl)-Tic-Phe-Phe-OH **(SEQ ID NO 23)**; H-Tyr(3-Br)-Tic-Phe-Phe-OH **(SEQ ID NO:24)**; H-Dmt-TicΨ[CH_2—NH]Phe-Phe-OH **(SEQ ID NO:25)**; H-Dmt-TicΨ[CH_2—NH]Phe-Phe-NH_2 **(SEQ ID NO:26)**; H-Tyr-TicΨ[CH_2—NCH_3]Phe-Phe-OH **(SEQ ID NO:27)**; H-Tyr-TicΨ[CH_2—NH]Hfe-Phe-OH **(SEQ ID NO:28)**; Tyr(NMe)-TicΨ[CH_2—NH]Hfe-Phe-OH[)] **(SEQ ID NO:29)**; H-Tyr-Tic-Phg-Phe-OH **(SEQ ID NO:30)**; H-Tyr-Tic-Trp-Phe-OH **(SEQ ID NO:31)**; H-Tyr-Tic-Trp-Phe-NH_2 **(SEQ ID NO:32)**; H-Tyr-Tic-His-Phe-OH **(SEQ ID NO:33)**; H-Tyr-Tic-2-Nal-Phe-OH **(SEQ ID NO:34)**; H-Tyr-Tic-Atc-Phe-OH **(SEQ ID NO:35)**; H-Tyr-Tic-Phe-Phe(pNO_2)-OH **(SEQ ID NO:36)**; H-Tyr-Tic-Trp-Phe(pNO_2)-OH **(SEQ ID NO:37)**; H-Tyr-Tic-Phe-Trp-NH_2 **(SEQ ID NO:38)**; H-Tyr-Tic-Phe-Phe-Val-Val-Gly-NH_2 **(SEQ ID NO:39)**; H-Tyr-Tic-Phe-Phe-Tyr-Pro-Ser-NH_2 **(SEQ ID NO:40)**; H-Tyr-Tic-Trp-Phe-Tyr-Pro-Ser-NH_2 **(SEQ ID NO:41)**; H-Tyr-Tic-Trp-Phe (pNO_2) -Tyr-Pro-Ser-NH_2 **(SEQ ID NO:42)** and H-Tyr-Tic-Phe-Phe-Leu-Nle-Asp-NH_2 **(SEQ ID NO:43)**.

The paragraph beginning at page 25, line 27 has been amended as follows:

Abbreviations in the aforementioned peptides of U.S. Patent 5,602,099 may be interpreted as follows: Aib=α-aminoisobutyric acid; Atc=2-aminotetralin-2-carboxylic acid; Boc=tert-butoxycarbonyl; Cpm=cyclopropylmethyl; DCC=dicyclohexyl-carbodiimide; DIEA=diisopropylethylamine; Dmt=2,6-dimethyltyrosine; Et=ethyl; Hex=hexyl; Hfe=homophenylalanine; HOBt=1-hydroxybenzotriazole; MVD=mouse vas deferens; 1-Nal=3-(1'-naphthyl)alanine; 2-Nal=3-(2'-naphthyl)alanine; Phe(pNO_2)=4-nitrophenylalanine; Phg=phenylglycine; Tic=1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; TIP=H-Tyr-Tic-Phe-OH **(SEQ ID NO:44)**; TIP-NH_2=H-Tyr-Tic-Phe-NH_2 **(SEQ ID NO:45)**; TIP(Ψ)=H-Tyr-TicΨ[CH_2-NH]Phe-OH **(SEQ ID NO:46)**; TIPP=H-Tyr-Tic-Phe-Phe-OH **(SEQ ID NO:14)**; TIPP-NH_2=H -Tyr-Tic-Phe-Phe-NH_2 **(SEQ ID NO:15)**; TIPP(Ψ)=H-Tyr-TicΨ[CH_2-NH]Phe-Phe-OH **(SEQ ID NO:47)**; Tyr(3-Br)=3-bromotyrosine; Tyr(3-Cl)=3-chlorotyrosine; Tyr(3-F)=3-fluorotyrosine; and Tyr(NαMe)=Nα-methyltyrosine.

Attorney Docket No. 9233.8DV2 PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
In re: Ekwuribe et al.
Serial No.: 09/430,735
Filed: 29 October 1999
For: *METHODS OF INDUCING ANALGESIA*

February 20, 2001

STATEMENT IN SUPPORT OF FILING A SEQUENCE LISTING UNDER 37 CFR § 1.821(f)

BOX SEQUENCE
Commissioner for Patents
Washington, DC 20231

Sir:

I hereby state that the content of the paper and computer readable copies of the Sequence listing, submitted concurrently herewith in accordance with 37 C.F.R. § 1.821(c) and (e), are the same.

Respectfully submitted,

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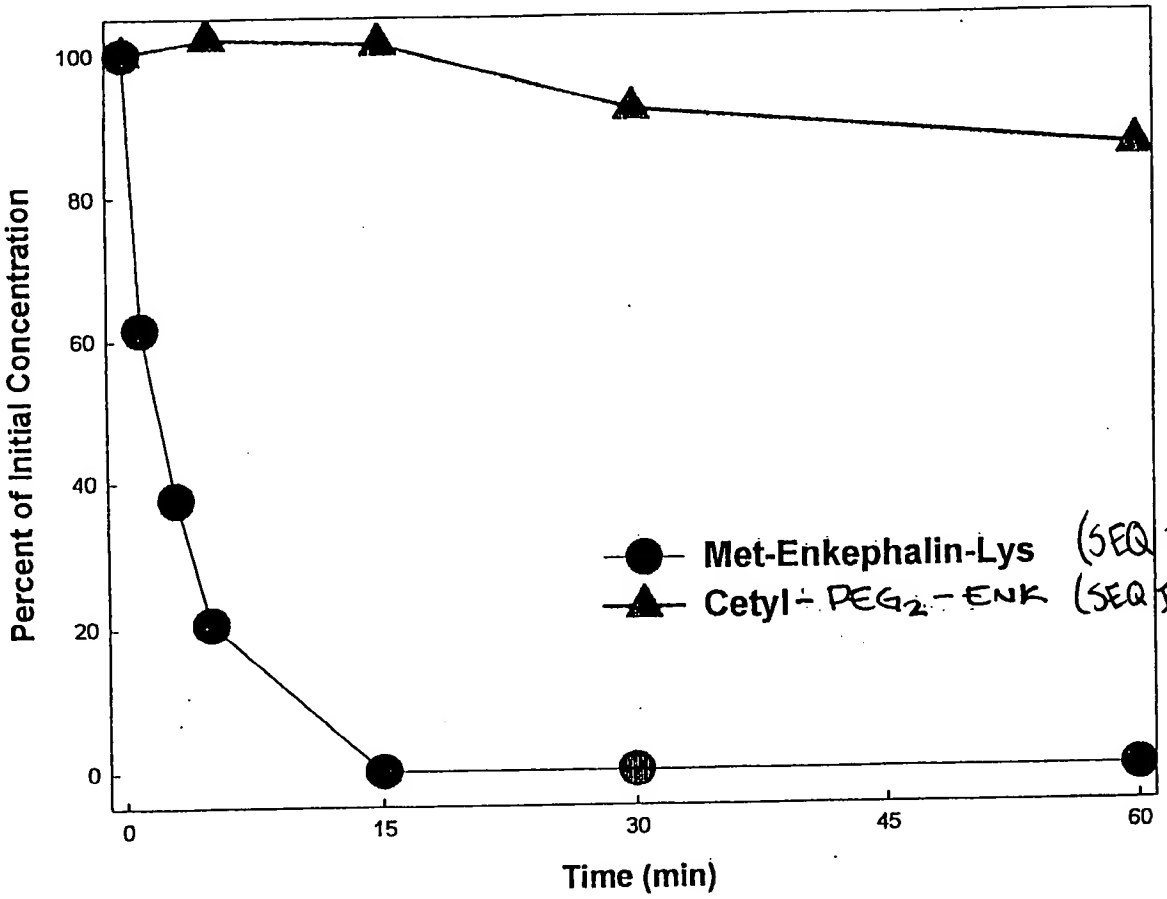
J. Michael Strickland
Date of Signature: February 20, 2001

Stability of Enkephalin and Cetyl-PEG_2-Enkephalin in Rat Brain Homogenate



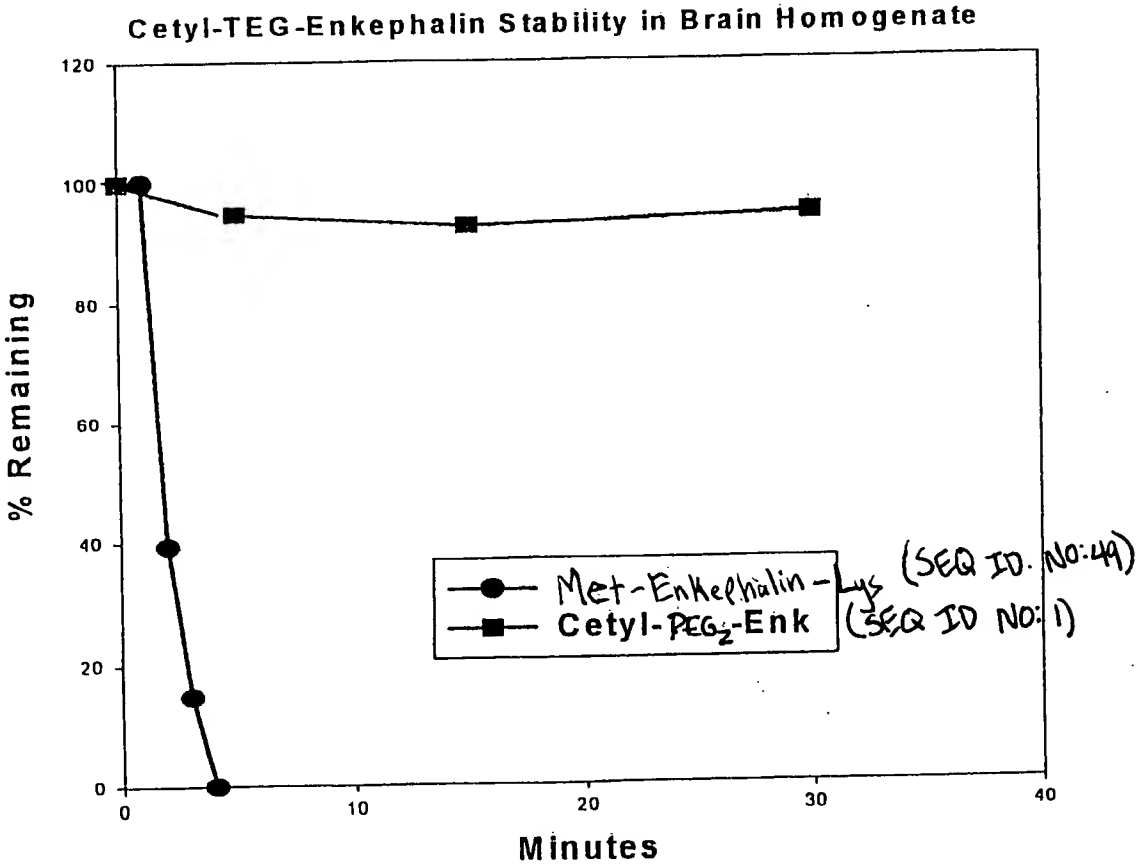
2 % Rat Brain in

PBS buffer, pH 7.4, 37 C

Peptide = 60 ug/mL

FIGURE 2

Stability of Cetyl- PEG_2 Enkephalin in Rat Brain Homogenate



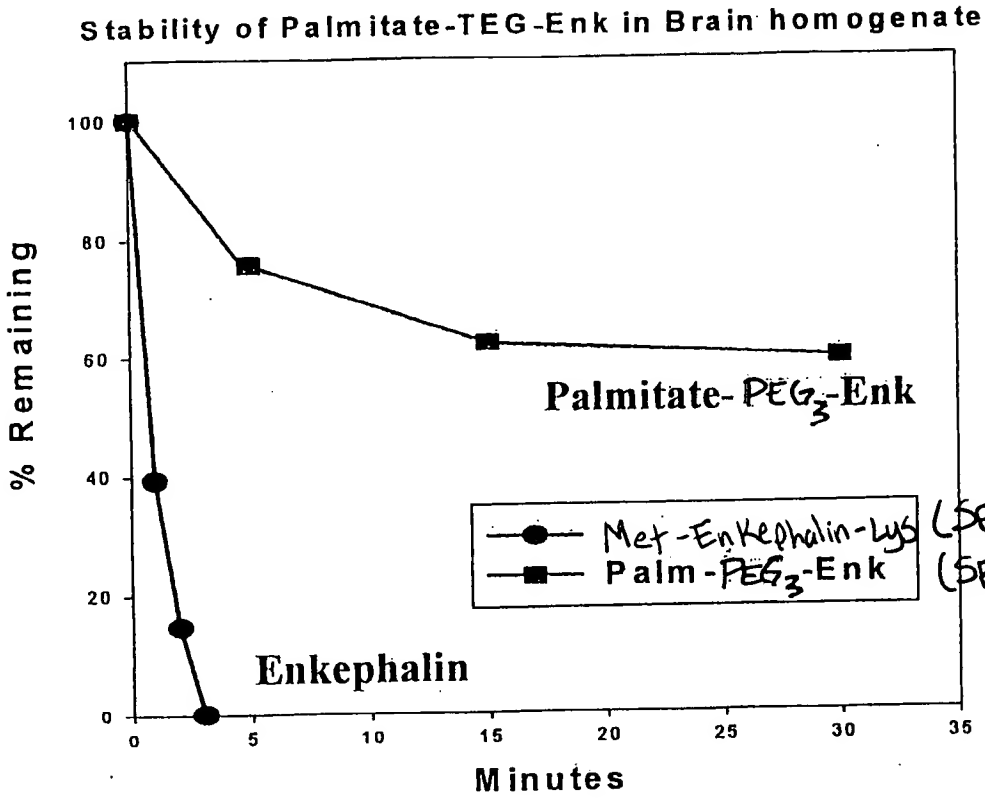
2 % w/v Rat brain in

PBS buffer, pH 7.4, 37 C

Peptide = 60 ug/mL

FIGURE 3

Stability of Palmitate-PEG3-Enkephalin in Rat Brain Homogenate



2% w/v Rat Brain in

PBS buffer, pH 7.4, 37 C

Peptide = 60ug/mL

FIGURE 4

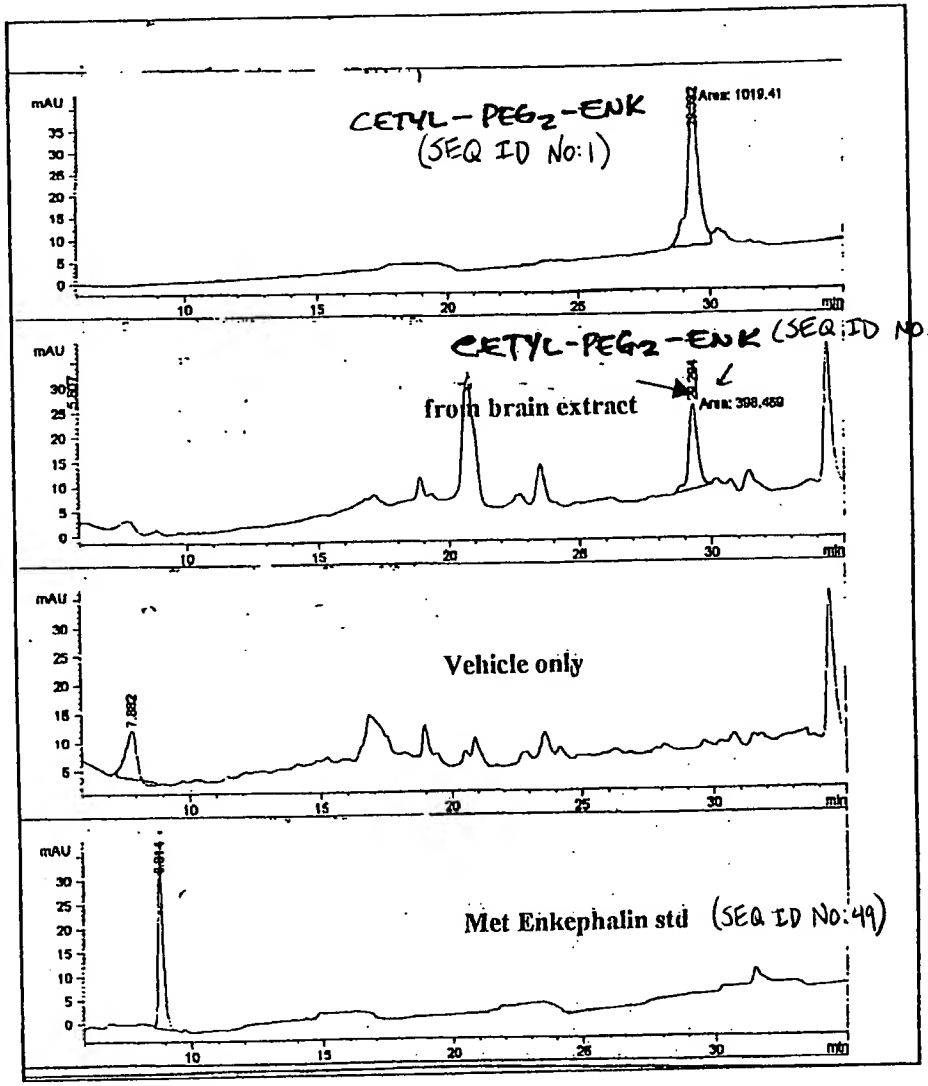
Isolation of Cetyl-PEG_2-Enkephalin (SEQ ID NO:1) from the Brain

FIGURE 5A

FIGURE 5B

FIGURE 5C

FIGURE 5D



HPLC conditions:
Column: C-18
Solvent: solvent A: IPA
solvent B: Water
+0.1% TFA
Gradient: linear

Naloxone Antagonism of Cetyl-PEG_2-Enkephalin-Induced Analgesia

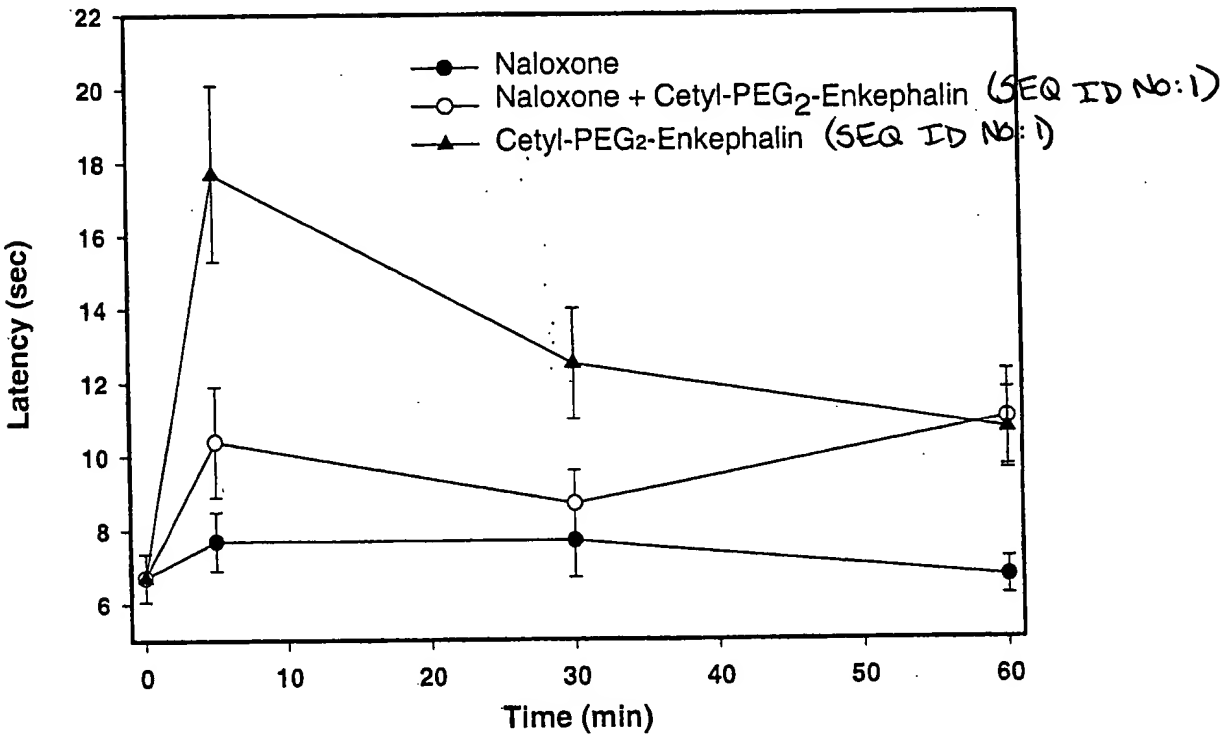


FIGURE 6

Analgesic Effect of a 5 mg/kg IV Dose of Cetyl-PEG_2-Enkephalin (SEQ ID No:1) Monoconjugate in the Rat Hot-Plate Assay

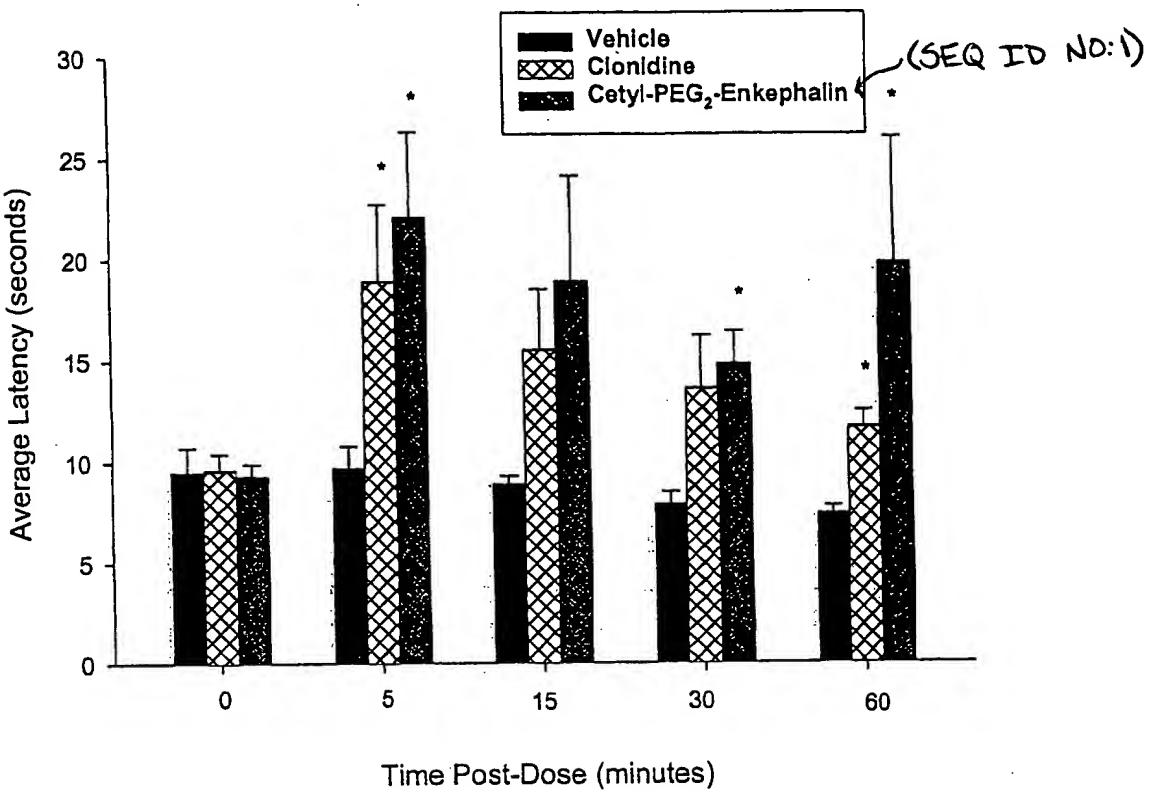


FIGURE 7

COMPARISON OF μ-RECEPTOR BINDING AFFINITY OF ENKEPHALIN CONJUGATES		
DRUG OR CONJUGATE	**DETAILED STRUCTURE**	**% SPECIFIC BINDING***
Naloxone	Naloxone	100
Enkephalin	Met-Enkephalin -Lys (SEQ ID NO:49)	67
Cetyl-ENK	Cetyl-PEG_2-ENK (SEQ ID NO:1)	100
Chol-ENK	Cholesterol-PEG_3-ENK (SEQ ID NO:1)	95
DHA-ENK	DHA-PEG_2-ENK (SEQ ID NO:1)	63
Palm-ENK	Palmitate-PEG_3-ENK (SEQ ID NO:1)	76
Cetyl-TEG-ENK	Cetyl-PEG_3-ENK (SEQ ID NO:1)	100

*Data are based on percent inhibition at a concentration of 100nM. The radioligand was DAMGO ([D-Ala2,N-Me-Phe-Gly5-ol]enkephalin) and naloxone served as the reference.

FIGURE 8